# COVER PAGE

## US EPA HPV Challenge Program

## Test Plan Submission

## O,O-Diethyl dithiophosphate (CAS No 298-06-6) and

## O,O-Diethyl dithiophosphate, sodium salt (CAS No 3338-24-7)



**Bayer CropScience LP**

**November 26, 2003**
**Revised October 2007**

# CONTENTS

# Tables

# US EPA HPV Challenge Program

# Test Plan Submission

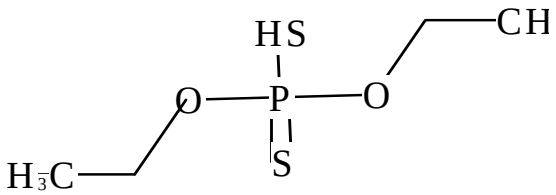
# O,O-Diethyl dithiophosphate (DEA; CAS No 298-06-6) and

# O,O-Diethyl dithiophosphate, sodium salt (DES; CAS No 3338-24-7)

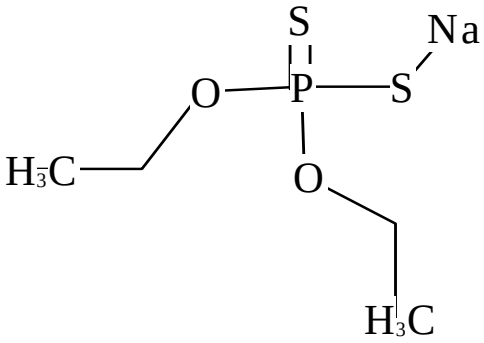
## 1 IDENTITY

### 1.1 Identification of the Substances

CAS Numbers: 298-06-6 and 3338-24-7
IUPAC Names: O,O-diethyl dithiophosphate and O,O-diethyl dithiophosphate, sodium salt
Molecular Formula: C4 H11 O2 P1 S2 and C4 H10 O2 P1 S2 Na1
Structural Formula:




DEA




DES

Molecular Weight: 186.23 and 208.21

DEA and DES were sponsored by Bayer in its original commitment to the HPV Program.

DEA and DES are used as intermediates in the production of an agricultural insecticide. DEA and DES are acid/salt pairs; Appendix B of the OECD "Guidance for the Use of Structure-Activity Relationships (SAR) in the HPV Chemicals Programme" provides examples from OECD SIDS cases and includes a specific example of acid-salt pairs (chloroacetic acid/sodium salt). In the case of the acid-salt pairs, no testing was considered necessary because the combined data for the acid/salt pair covered all of the SIDS endpoints. Similar to the SIDS approach for chloroacetic acid/sodium salt, the existing data for DEA and DES, which are acid/salt pairs, indicate that data sharing between the two substances is appropriate.

### 1.2 Physico-Chemical properties

**Table 1** Summary of physico-chemical properties

| **Property** | **DEA CAS 298-06-6** | **DES CAS 3338-24-7** |
|---|---|---|
| Physical state | Liquid | Liquid |
| Melting point | -10 ºC(*) EpiWin 3.11 | 182-183 ºC McEwen, 1982 |
| Boiling point | 105-108 ºC at 20 hPa Merck KGaA (no date) | Decomposes (150 ºC) Bayer, 1991 |
| Vapour pressure | No data available [.077 hPa at 25 ºC EpiWin 3.11] | No data available [3.95E-8 hPa at 25 ºC EpiWin 3.11] |
| Water solubility | No data available [Insoluble Merck KGaA (no date)] | No data available [97,750 mg/L at 25 ºC EpiWin 3.11] |
| Partition coefficient n-octanol/water (log value) | 1.17 Advanced Chemistry Development (no date) | -.46 at 25 ºC EpiWin 3.11 |
| Dissociation constant pKa | 1.6 Kabachnik et al., 1960 | No data available |

(*)Experimental Database Structure Match

Conclusion

In order to complete the physical chemical properties profile for these substances, vapour pressure (DEA and DES) and water solubility (DEA and DES) studies (OECD TG 105 and 104, respectively) will be conducted.

## 2 ENVIRONMENTAL EXPOSURE AND FATE

DEA and DES behave similarly in the environment.

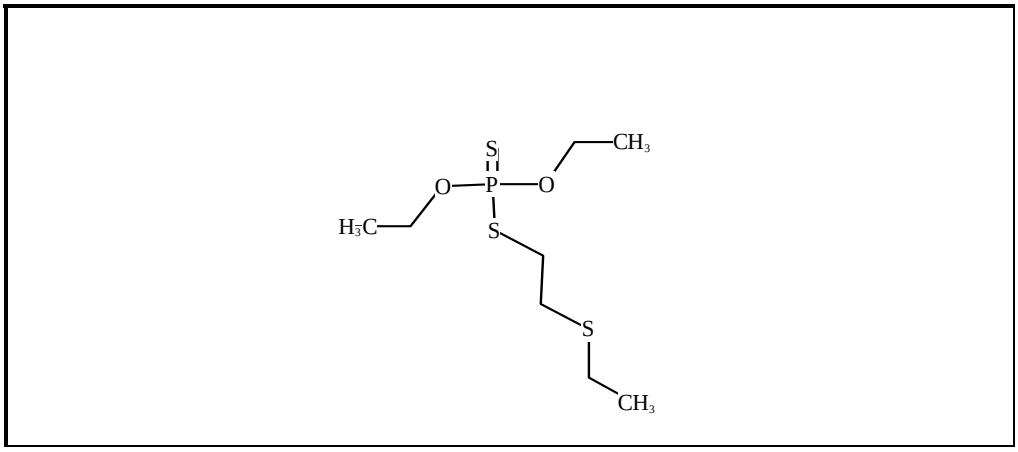
### 2.1 Photodegradation

DEA and DES in air are not expected to undergo direct photolysis, but may undergo indirect photolysis through hydroxyl radical oxidation. The hydroxyl radical reaction was calculated using AOPWIN® ver. 1.91 (EpiWin, v.3.11). The overall OH rate constants for DEA and DES are 91.6286 E-12 cm3/molecule-sec with an estimated half-life of 0.117 days.

### 2.2 Stability in Water

Studies were not located regarding the abiotioc hydrolysis of DEA and DES. However, hydrolysis is not expected to be a primary route of degradation of these substances based on analogy to a structurally related substance, Disulfoton (CAS 298-04-4). Disulfoton is stable to hydrolysis at 20$^{o}$ C at pH 5, 7, and 9, but hydrolyzes more rapidly at higher temperatures (Patterson, 2003). Estimated hydrolysis half-lives for Disulfoton were 103 days at 25 ºC and pH 7 (Ellington et al. 1988) and 170 days at 11 ºC and pH 7.9 (Wanner et al., 1989).

**Table 2** Structure of Disulfoton




### 2.3 Transport between Environmental Compartments

The EQC Level III Fugacity model (EpiWin, v. 3.11) was used to evaluate the fate, transport and distribution of DEA and DES between environmental matrices. Level III fugacity modelling, using loading rates of 1000 kg/h each for air, soil and water, shows the following percent distribution when it is released simultaneously to all three compartments: DEA: Air = 0.879%, Soil = 68.3%, Water = 30.7 %, and Sediment = 0.145%, and DES: Air = 8.79E-6%, Soil = 53.7%, Water = 46.2 %, and Sediment = 0.089 %.

### 2.4 Biodegradation

In a MITI-I (OECD TG 301C) study, DEA was not readily biodegradable (NITE, 2002). DES is also expected to not be readily biodegradable.

Conclusion

Additional environmental fate testing is not warranted.

## 3 HUMAN HEALTH HAZARDS

### 3.1 Effects on Human Health

DES would be expected to quickly dissociate to sodium and DEA in an aqueous environment such as the mammalian body. Upon the dissociation of DES, sodium would not be a significant factor in the metabolism or toxicity of DEA and thus, the systemic toxicity of DES would be equivalent to DEA on a molar basis. Therefore, the mammalian toxicological data for DEA are adequate for the

evaluation of the potential hazards of the sodium salt of DES. The similarity of the acute toxicity and irritation data for DEA and DES support this premise. It is unclear as to the reason for the discrepancy between results of the bacterial mutagenicity tests for these substances.

### 3.1.1 Acute Toxicity

Studies in Animals

*Inhalation*

Six groups of rats (5/sex/dose) were exposed for 4 hours to an atmosphere of DEA at concentrations of 0.98, 1.02, 10.4, 1.35, 1.60, and 2.10 mg/L (Monsanto, 1981; RL = 2). The gross signs of toxicity observed during the exposures were clear nasal discharge, lacrimation, breathing difficulties, hypoactivity and fur discoloration (fur covered with test material). During the 14-day post-exposure period, hypoactivity, breathing difficulties, chromodacryorrhea around the mouth, nose and eyes, initial loss in body weight, and death were observed. Infrequently during these two weeks, abrasions, edema and swelling about the nose and mouth, wheezing, dehydration, emaciation, clear nasal discharge, lacrimation, piloerection, and tremors were observed. Red blood cell and plasma cholinesterase levels were increased 115% and decreased 30%, respectively, in six male rats exposed to 0.98 mg/L of air. The most frequent necropsy findings observed in rats, sacrificed either in extremis or sacrificed per design at the end of the post-exposure period, were petechial hemorrhage of the thymus and lungs, alopecia, chromodacryorrhea and abrasions about the mouth and nose. The mean lethal concentration (4 hr LC50; combined) was = 1.89 mg/L.

Six male rats were exposed to 0.7 mg/L DEA for 6 hrs (Younger Labs, 1979; RL = 2). Labored breathing, ocular erythema, increasing weakness was noted between 1 and 15 minutes exposure; tremors, nasal bleeding, and one death occurred between 15-30 minutes of exposure. The remaining animals appeared normal for the remaining duration of the exposure. Hemorrhagic lungs were noted in the one animal that died; no findings were noted in the remaining surviving animals.

Acute inhalation data were not located for DES.

*Dermal*

DEA was applied undiluted to the skin of rabbits for 24 hours at doses of 1000, 2000, 3160, and 5010 mg/kg bw (Younger Labs, 1979; RL = 2). There was one animal per dose. Weight loss; increasing weakness, ocular discharge; collapse, and death were noted. Lung hyperemia, enlarged gall bladder, and darkened spleen were noted in animals that died; there were no findings in survivors. The dermal LD50 of DEA was > 2000 mg/kg bw.

DES was applied undiluted to the skin of four rabbits at a dose of 2000 mg/kg bw (Mobay, 1972; RL = 2). The skin of one male and one female animal was abraded. There were no clinical signs or deaths. The LD50 of DES is > 2000 mg/kg bw.

*Oral*

Groups of male and female rats (total of five rats/dose group) were gavaged at DEA doses of 1260, 1580, 2000, and 2510 mg/kg bw (Younger Labs, 1979; RL = 2). Signs of toxicity included weight loss (one to four days in survivors); increasing weakness, collapse and death. Hemorrhagic lungs, liver discoloration, and acute gastrointestinal inflammation were noted in animals that died; there were no findings at necropsy in surviving animals. The LD50 (combined) = 1400 mg/kg bw.

Reliable acute oral data were not located for DES.

**Table 3** Summary of acute toxicity

| Route of exposure | DEA CAS 298-06-6 | DES CAS 3338-24-7 |
|---|---|---|
| Inhalation (LC50) rat | 1.89 mg/L (4 hr; combined) | No data |
| Dermal (LD50) rat | > 2000 mg/kg bw (combined) | >2000 mg/kg bw (combined) |
| Oral (LD50) rat | 1400 mg/kg bw (combined) | No data |

Conclusion

The mean lethal concentration (4 hr LC50; combined) of DES was = 1.89 mg/L data were not located for DES. The dermal LD50 of both DEA and DES were > 2000 mg/kg bw. The oral LD50 of DEA was 1400 mg/kg bw; reliable acute oral data were not located for DES.

### 3.1.2 Irritation

Skin Irritation

*Studies in Animals*

0.5 ml of undiluted DEA was applied to the clipped, intact skin of albino rabbits and removed after 24 hours (Younger Labs, 1962; RL = 2). Slight edema and a whitish appearance developed on the skin within one hour. Edema sufficient to outline the treated areas was noted in 4 hours. The skin remained whitish, a condition often observed in the first few hours of severe tissue injury. Overnight there was severe swelling and obvious evidence of tissue necrosis. The destroyed tissue turned red and gradually dried after several days. The compound was classified as a corrosive skin irritant.

DEA (0.5 ml) was applied undiluted to the skin of 6 rabbits for a 24-hr exposure period and observed for at least 10 days (Younger Labs, 1979; RL = 2). A maximum irritation score was recorded in all animals within 24 hours. Loosening about edges of scab in 7 to 10 days showed the depth of the injury. DEA was considered highly corrosive under the conditions of this study.

No skin irritation data were located for DES.

Eye Irritation

*Studies in Animals*

0.1 ml of undiluted DEA was placed in the conjunctival sac of the right eye of each of three rabbits and observations made over a period of several days of inflammation (Younger Labs, 1969; RL = 2). The eyes were rinsed with warm isotonic saline solution in animal #1 after 24 hours, in animal #2 after ten seconds, and in animal #3 after 4 seconds. The animals reacted immediately upon application and the cornea became opaque even in the eye of the animal with the 4 second exposure. There was rapid edema extending for a considerable area around the eye resulting in the lids being closed in all instances in less than one hour. Copious lacrimation, beefy red conjunctivae and invisible iris indicating loss of vision produced the maximum irritation score for all three exposures. DEA was considered a corrosive eye irritant under the conditions of this study.

Reliable eye irritation studies were not located for DES. However, studies considered RL =4 (not assignable) suggest DES is a moderate to highly irritating eye irritant.

Conclusion

DEA is a corrosive skin and eye irritant. Similar findings are expected for DES.

### 3.1.3 Repeated Dose Toxicity

Repeat dose toxicity data were not located for DEA or DES.

Conclusion

An oral gavage OECD TG 422 study is planned for DEA; this data will be read across to DES.

### 3.1.4 Mutagenicity

*In vivo* Studies

No data were located for DEA or DES.

*In vitro* Studies

In a standard Ames test, *Salmonella typhimurium* TA1535, TA1537, TA1538, TA98 and TA100 were exposed to DEA at concentrations of 50, 100, 250, 500, and 1000 ug/plate, in the presence and absence of metabolic activation (FMC, 1986a; RL = 1). Cytotoxicity was observed at concentrations >= 3333.3 ug/plate. Under the conditions of the study, DEA did cause a positive response in TA1535 both with and without metabolic activation and in TA100 without metabolic activation. In a standard Ames test, *Salmonella typhimurium* TA1535, TA1537, TA1538, TA98 and TA100 were exposed to DEA at concentrations of 250, 500, 1000, 2500, and 5000 ug/plate, in the presence and absence of metabolic activation (FMC, 1986b; RL = 2). Cytotoxicity was observed at concentrations > 5000 ug/plate. DEA induced a positive mutagenic response in strain TA100 without activation and in strain TA1535, both with and without activation. All other assays were negative.

In a standard Ames test, *Salmonella typhimurium* TA98, TA100, TA1535, TA1537 and TA1538 were exposed to DES at concentrations of 100, 333, 1000, 3333 and 10,000 ug/plate, in the presence and absence of metabolic activation (FMC, 1986c; RL = 1). Cytotoxicity was observed at concentrations > 10,000 ug/plate. Under the conditions of the study, the test material did not cause a positive response in any of the tester strains with or without metabolic activation.

Conclusion

An in vitro chromosome aberration study (OECD TG 473) is planned with DEA; this data will be read across to DES.

### 3.1.5 Toxicity for Reproduction

No data were located for DEA or DES.

Conclusion

An oral gavage OECD TG 422 study is planned for DEA; this data will be read across to DES.

## 4 HAZARDS TO THE ENVIRONMENT

DES would be expected to quickly dissociate to sodium and DEA in an aqueous environment. Upon the dissociation of DES, sodium would not be a significant factor in the metabolism or toxicity of

DEA and thus, the aquatic toxicity of DES would be equivalent to DEA on a molar basis. Therefore, the ecological toxicological data for DEA are adequate for the evaluation of the potential hazards of the sodium salt of DES. The similarity of the acute fish toxicity data for DEA and DES support this premise.

### 4.1 Aquatic Effects

Acute Toxicity Test Results

*Oryzias latipes* were exposed to DEA for 48 hrs as part of a bioaccumulation test (NITE, 2002; RL = 2). The LC50 was 440 mg/L. *Salmo gairdneri* were exposed to DES for 96 hrs (Fuerstenau and Wakawa, 1974; RL = 2). The LC50s were = 400 - 410 ppm at 12 $^{o}$C and = 310 - 330 ppm at 16 $^{o}$C.

*Daphnia magna* were exposed to DEA for 24 hrs following OECD TG 202 (Galli et al., 1994; RL = 2). The EC50 was 0.54 mg/L.

Data were not located for acute toxicity to algae for either DEA or DES.

Conclusion

An OECD TG 201 will be conducted with DEA; this study will be read across to DES.

## 5 RECOMMENDATIONS FOR THE DEA/DES TEST PLAN

In order to complete the physical chemical properties profile for these substances, vapour pressure (DEA and DES) and water solubility studies (DEA and DES) (OECD TG 105 and 104, respectively) will be conducted. All environmental fate endpoints have been fulfilled. An oral gavage OECD TG 422 study is planned for DEA to fulfil the repeated dose, reproductive and developmental endpoints; this data will be read across to DES. An in vitro chromosome aberration study (OECD TG 473) is planned with DEA; this data will be read across to DES. An OECD TG 201 (acute toxicity to algae) will be conducted with DEA; this study will be read across to DES.

## 6 REFERENCES

Advanced Chemistry Development (ACD) (no date) Software Solaris v.4.67 (copyright 1994-2002 ACD)

BAYER CORPORATION (1991) MSDS Diethyl Salt Solution AGRICULTURE DIVISION P.O. Box 4913 Hawthorn Road Kansas City, MO 64120-0013

Ellington JJ, Stancil FE, Payne WD, et al. 1988. Measurement of hydrolysis rate constants for evaluation of hazardous waste land disposal: Vol. 3. Data on 70 chemicals. Engineering Research Laboratory, U.S. Environmental Protection Agency, Athens, GA. EPA/600/S3-88-028. NTIS PB38-234842/AS. Cited in ATSDR Toxicological Profile for Disulfoton (1995) http://www.atsdr.cdc.gov/toxprofiles/tp65.html#bookmark12

EPIWin Modeling Program. (version 3.11) (2000). Developed by the EPA's Office of Pollution Prevention Toxics and Syracuse Research Corporation (SRC). copyright 2000 U.S. Environmental Protection Agency

FMC Corporation (1986a) O,O-DIETHYL PHOSPHORODITHIOATE: Salmonella/Mammalian-Microsome Plate Incorporation Mutagenicity Assay (Ames Test). Study Number A85-1676. Fiche Number: 0000465-2 Cited in NISC BiblioLineMerck KGaA (no date) Frankfurter Str. 250, D-64293 Darmstadt, Germany. www.chemdata.de/

FMC Genetic Toxicology Laboratory (1986b) O,O-Diethyl Phosphorodithioate: Preliminary results for a second Ames Salmonella/microsome Mutagenicity Test with A New Sample of O,O-Diethyl Phosphorodithioate w/Letter and EPA Acknowledgement Letter. EPA Document No. FYI-OTS-0386-0465, Fiche No. OTS0000465-0. Cited in NISC BiblioLine

FMC Corporation (1986c) Phosphorodithioic acid, O,O-diethyl ester, sodium salt: Salmonella/Mammalian-Microsome Plate Incorporation Mutagenicity Assay (Ames Test). Study Number A85-1802. Fiche Number: 0000465-1 Cited in NISC BiblioLine

Fuerstenau MC, Wakawa BM, et al. (1974). Toxicity of selected sulfhydryl collectors to rainbow trout. Transactions. Society of Mining Engineers. 256(4): 337-341.

Galli R, Rich H W, Scoltz R. (1994). Toxicity of organophosphate insecticides and their metabolites to the water flea, Daphnia magna, the Microtox test and an acetylcholinesterase inhibition test. Aquatic Tox. 30:259-269.Mobay Chemical Corporation. (1972). CHEMAGRO Agricultural Division Study Report No. 35287

KABACHNIK M.I., T. A. MASTRUKOVA, A. E. SHIPOV and T. A. MELENTYEVA (1960) THE APPLICATION OF THE HAMMETT EQUATION TO THE THEORY OF TAUTOMERIC EQUILIBRIUM THIONE-THIOL EQUILIBRIUM, ACIDITY, AND STRUCTURE OF PHOSPHORUS THIO-ACIDS. Tetrahedron. 1960. Vol. 9. pp. 10 to 28.

Institute of Organo-Element Compounds, U.S.S.R. Merck KGaA (no date) Frankfurter Str. 250, D-64293 Darmstadt, Germany. www.chemdata.de/

McEwen, W.E.(1982) Phosphorus and Sulfur and the Related Elements, 1982, W 13(1), p 35-40.

Mobay Chemical Corporation. (1972). CHEMAGRO Agricultural Division Study Report No. 35287

MONSANTO AGRIC CO (1981) O,O-DIETHYL PHOSPHORODITHIOATE INITIAL SUBMISSION: ACUTE INHALATION LC50 OF O,O'-DIETHYL PHOSPHORODITHIOATE (ETHYL THIOACID) IN SPRAGUE-DAWLEY RATS (FINAL REPORT) WITH ATTACHMENTS AND COVER LETTER DATED 040692. Cited in NISC BiblioLine.

National Institute of Technology and Evaluation (NITE) (2002) Biodegradation and Bioconcentration of Existing Chemical Substances under the Chemical Substances Control Law http://www.safe.nite.go.jp/data/sougou/pk_e_search_frm.html?cas_no=298-06-6

Patterson, M (2003) Disulfoton Analysis of Risks to Endangered and Threatened Salmon and Steelhead. USEPA, Environmental Field Branch Office of Pesticide Programs. http://www.epa.gov/oppfead1/endanger/effects/disulfoton-analysis.pdf

Wanner U, Egli, T., Fleischmann T, et al. 1989. Behavior of the insecticides disulfoton and thiometon in the Rhine River.A chemodynamic study. Environmental Science and Technology 23:1232-1242. Cited in ATSDR Toxicological Profile for Disulfoton (1995) http://www.atsdr.cdc.gov/toxprofiles/tp65.html#bookmark12

Younger Laboratories (1962) O,O-DIETHYL PHOSPHORODITHIOATE INITIAL SUBMISSION: TOXICOLOGICAL INVESTIGATION OF O,O-DIETHYLPHOSPHORODITHIOIC ACID ETHYL THIOACID WITH COVER LETTER DATED 061092. Fiche No. 0536767 and No. 0543125 Cited in NISC BiblioLine

Younger Laboratories (1979) O,O-DIETHYL PHOSPHORODITHIOATE INITIAL SUBMISSION: LETTER FROM MONSANTO CO TO US EPA SUBMITTING ENCLOSED SUMMARY CONCERNING DIETHYL PHOSPHORODITHIOC ACID ACUTE EYE AND

SKIN IRRITATION STUDIES WITH ATTACHMENT. Fiche No. 0543123 Document Number: 88-920004808 Cited in NISC BiblioLine